Original Article

Esophageal cancer in patients under 50: a SEER analysis

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Background: Concomitant with rising rates of esophageal adenocarcinoma, there has been a significant increase of diagnoses among relatively younger individuals. However, most studies that focus on esophageal cancer (EC) in younger patients have had small sample sizes of patients treated at a single institute. The aim of this study was to analyze the clinical characteristics, outcomes and independent prognostic factors for EC in patients under 50-year-old using a large, multi-center dataset.

Methods: The national Surveillance, Epidemiology, and End Results (SEER) database was analyzed for EC reported from 2004 to 2013. Patients were divided into two groups, those under 50-year-old and those 50 years or older, and comparisons were made regarding demographics, histology, stage distribution, treatment, overall survival (OS), and esophageal cancer-specific survival (ECSS). Multivariate Cox proportional hazard regression analyses were also used to identify independent prognostic factors.

Results: Among the 16,544 eligible patients, 1,385 (8.37%) were under 50 and 15,159 (91.63%) were over 50. Compared with the older group, patients under 50 were characterized by a higher frequency of males, lower esophagus involvement, adenocarcinoma histology, stage III/IV disease, and receiving esophagectomy or radiation therapy. The stage-wise OS and ECSS were significantly better in the younger group (P<0.001). The multivariate analysis indicated that African-American heritage, grade III or IV, later stage, and not undergoing surgical or radiation therapy were independent negative prognostic factors of ECSS for patients under 50.

Conclusions: EC patients under 50-year-old had distinctive clinicopathological characteristics compared with patients over 50-year-old. Despite more often presenting with stage III and IV disease, survival rates were better in the younger cohort. Prognostic factors for ECSS in patients under 50 differed from those in all age patients.

Keywords: Surveillance, Epidemiology, and End Results (SEER); esophageal cancer (EC); young patients

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Introduction

There were approximately 455,800 new esophageal cancer (EC) diagnoses and 400,200 deaths due to the malignancy in 2012 (1), making it one of the most common cancers worldwide. In the United States there were an estimated 16,980 new EC diagnoses and 15,590 deaths in 2015 (2). Currently, the 5-year survival rate of EC is approximately 20% (3).

Recent studies have shown that increasing numbers of young patients are being diagnosed with EC, and predominantly esophageal adenocarcinoma (4-6). However, the clinical characteristics and outcomes for EC in the young population have not been well described. There are conflicting data on the distributions of histological subtype and clinical stage at diagnosis (7-9). Furthermore, the majority of published data regarding EC in young patients originate from single-institution retrospective studies, and it remains controversial whether young EC patients have better or worse outcomes than older patients (7-12). Additionally, most of these studies have used small numbers of young patients, and some have only evaluated patients with esophageal adenocarcinoma.

It is essential to determine if the clinical characteristics and/or survival rates of younger EC patients differs from older patients in a large-scale study. Therefore, the national Surveillance, Epidemiology and End Results (SEER) database, which collected EC patient data from 2004 to 2013 was used to study the clinical characteristics, outcomes and independent prognostic factors for EC in patients under 50 years old.

Methods

Patients

The SEER database is compiled by the National Cancer Institute and covers approximately 28% of the United States population. Ethical approval was obtained from participating institutions through their respective institutional review boards. We analyzed the SEER Cancer Incidence Public-Use Database that was submitted in November 2013, and data regarding EC (site codes C15.0–C15.9) were extracted for the years 2004 to 2013. The exclusion criteria were records lacking microscopically confirmed diagnoses or diagnoses made during autopsy or by death certificate, records lacking age, race, or sex, site of cancer, differentiation grade, stage, surgery, radiation information, and those lacking patient survival times. All malignancies were staged according to the AJCC 6th edition. Surgery techniques included endoscopic treatment and esophagectomy; radiation included any method of radiation therapy.

A total of 16,544 EC patients matching the specified criteria were included in the final analysis. The individual data retrieved for each case included age at diagnosis, gender, race, year of diagnosis, site of cancer, differentiation grade, tumor histology, stage, treatment modality (radiotherapy/surgery), cause-specific death classification, vital status and survival time. Finally, the entire patient population was divided into two groups: less than 50 years and 50 years or older at diagnosis.

Statistical analysis

The Chi-square test was used to evaluate the statistical significance of differences in gender, race, year of diagnosis, site of cancer, differentiation grade, tumor histology, stage, and treatment modality among the two age groups. Overall survival (OS) was defined as the time from diagnosis to death from any cause, and patients that are currently alive were censored at the time of last recording. EC-specific survival (ECSS) was defined as the time from diagnosis to EC-related death. OS and ECSS were estimated using the Kaplan–Meier method and compared by log-rank test. Multivariate Cox proportional hazard regression was used to determine independent prognostic factors, and a hazard ratio (HR) and corresponding 95% confidence interval (CI) were calculated. Statistical analyses were performed using SEER*stat and SPSS 20.0. All statistical tests were two sided and $P<0.05$ was considered statistically significant.

Results

Demographics

A total of 16,544 patients met the entry criteria of this study. The median age was 65-year-old, and the median [interquartile range (IQR)] follow-up time for ECSS was 9 [4–22] months. There were 1,385 patients (8.37%) younger than 50, and 15,159 patients (91.63%) over 50. The distribution of each age is shown in *Figure S1*. The proportion of women with EC was significantly lower in the younger group than in the older group (15.2% *vs.* 19.1%; $P<0.001$). There was a higher proportion of African-Americans in the younger group than the older group (11.3% *vs.* 9.6%; $P<0.001$). Additionally, there was a significantly lower proportion of young patients diagnosed in 2009–2013 compared with the previous years in the dataset (47% *vs.* 51.4%; $P<0.001$) (*Table 1*).

Site of cancer and Differentiation grade

The distribution of cancer sites was significantly different between the younger and older groups. Lower esophagus

Table 1 Description of the SEER population of patients with esophageal cancer by age at diagnosis

Characteristic	Age group (years)				P
	<50 (n=1,385)		≥50 (n=15,159)		
	No.	%	No.	%	
Gender					<0.001
Male	1,175	84.8	12,271	80.9	
Female	210	15.2	2,888	19.1	
Race					0.116
White	1,161	83.8	12,977	85.6	
African-American	157	11.3	1,458	9.6	
Other	67	4.8	724	4.8	
Year					0.002
2004–2008	734	53	7,369	48.6	
2009–2013	651	47	7,790	51.4	
Site of cancer					<0.001
Upper esophagus	52	3.8	820	5.4	
Middle esophagus	173	12.5	2,819	18.6	
Lower esophagus	1,160	83.6	11,520	76	
Differentiation grade					0.843
Grade I	78	5.6	835	5.5	
Grade II	544	39.3	6,075	40.1	
Grade III or IV	763	55.1	8,249	54.4	
Histology					<0.001
Squamous	285	20.6	4,350	28.7	
Adenocarcinoma	1,004	72.5	9,953	65.7	
Others	96	6.9	856	5.6	
Stage					<0.001
I	127	9.2	2,568	16.9	
II	247	17.8	3,283	21.7	
III	339	24.5	3,559	23.5	
IV	672	48.5	5,749	37.9	
Surgery					<0.001
Endoscopic	18	1.3	383	2.5	
Esophagectomy	500	36.1	4,450	29.4	
No	867	62.6	10,326	68.1	
Radiation therapy					0.341
Yes	842	60.8	9,017	59.5	
No	543	39.2	6,142	40.5	

NOS, not otherwise specified; SEER, Surveillance, Epidemiology, and End Results.

involvement was more prevalent in patients under 50 (83.6% *vs.* 76%; P<0.001). In contrast, upper and middle esophageal disease were more prevalent in the older group (3.8% *vs.* 5.4%; P<0.001; and 12.5% *vs.* 18.6%; P<0.001, respectively). Additionally, there was no significant difference in the differentiation grades between patients under 50 and patients over 50 (P=0.843).

Histology and staging

There were considerable differences in the distribution of tumor histologies between the two groups. Most strikingly, adenocarcinoma cases were more prevalent in the younger patients (72.5% *vs.* 65.7%; P<0.001). In contrast, squamous cell carcinoma accounted for 20.6% of patients under 50, but 28.7% of patients over 50 (P<0.001). The distribution of tumor staging was also significantly different between the two groups. The younger group had a higher proportion of stage III and IV disease than the older group, whereas the older group had a higher proportion of patients with stage I and II disease (P<0.001) (*Table 1*).

Therapy

The use of surgery and radiation therapy was also significantly different between the two groups. The proportion of patients that underwent esophagectomy was significantly higher in younger group (36.1%) than the older group (29.4%) (P<0.001); 1.3% of the younger group and 2.5% of the older group received endoscopic therapy (P<0.001). However, there was no difference in radiation therapy (P=0.341).

Survival and prognostic factors

The stage-wise, overall and cancer-specific survival rates

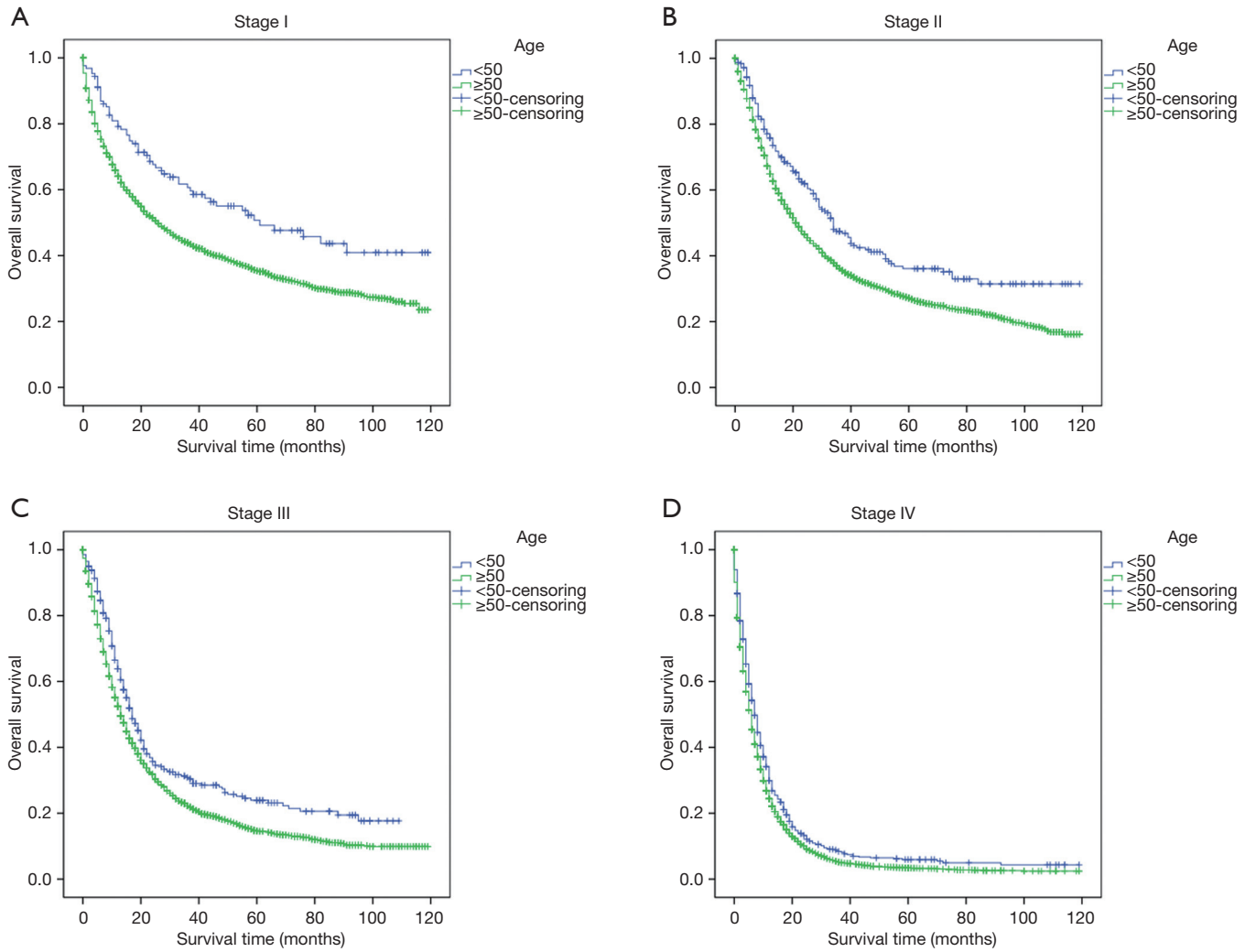

Figure 1 Kaplan-Meier curves comparing stage-wise overall survival between patients under 50 years and patients 50 years or older.

were higher for younger patients than older patients (P<0.001; *Figures 1*,*2*). A multivariate analysis was performed to control for the effects of age, race, year of diagnosis, histology, site of cancer, differentiation grade, tumor stage and treatment modality on ECSS (*Table 2*). The results of the multivariate analysis indicated that age <50 years was an independent predictor of improved ECSS (HR: 0.881; 95% CI: 0.824–0.943; P<0.001). The independent HR of death was highest for patients with stage IV disease (HR: 2.681; 95% CI: 2.504–2.870; P<0.001). African-Americans (HR: 1.134; 95% CI: 1.061–1.212; P<0.001), patients with squamous cell carcinoma (HR: 1.059; 95% CI: 1.002–1.119; P<0.001), grade III or IV (HR: 1.631; 95% CI: 1.475–1.802; P<0.001) and year of diagnosis between 2004 and 2008 (HR: 1.193; 95% CI: 1.148–1.240; P<0.001) were also significant independent negative prognostic factors. Patients with Endoscopic therapy (HR: 0.306; 95% CI: 0.254–0.369; P<0.001) or Esophagectomy (HR: 0.346; 95% CI: 0.328–0.365; P<0.001) and radiation therapy (HR: 0.634; 95% CI: 0.609–0.660; P<0.001) were significant independent predictors of improved ECSS (*Table 2*).

In the group of younger patients, the multivariate analysis indicated that significant independent negative prognostic factors included African-American (HR: 1.508; 95% CI: 1.238–1.837; P<0.001), grade III or IV (HR: 2.073; 95% CI: 1.456–2.953; P<0.001), later stage (P<0.001). Moreover, endoscopic treatment (HR: 0.261; 95% CI: 0.096–0.708; P<0.001), esophagectomy (HR: 0.323; 95%

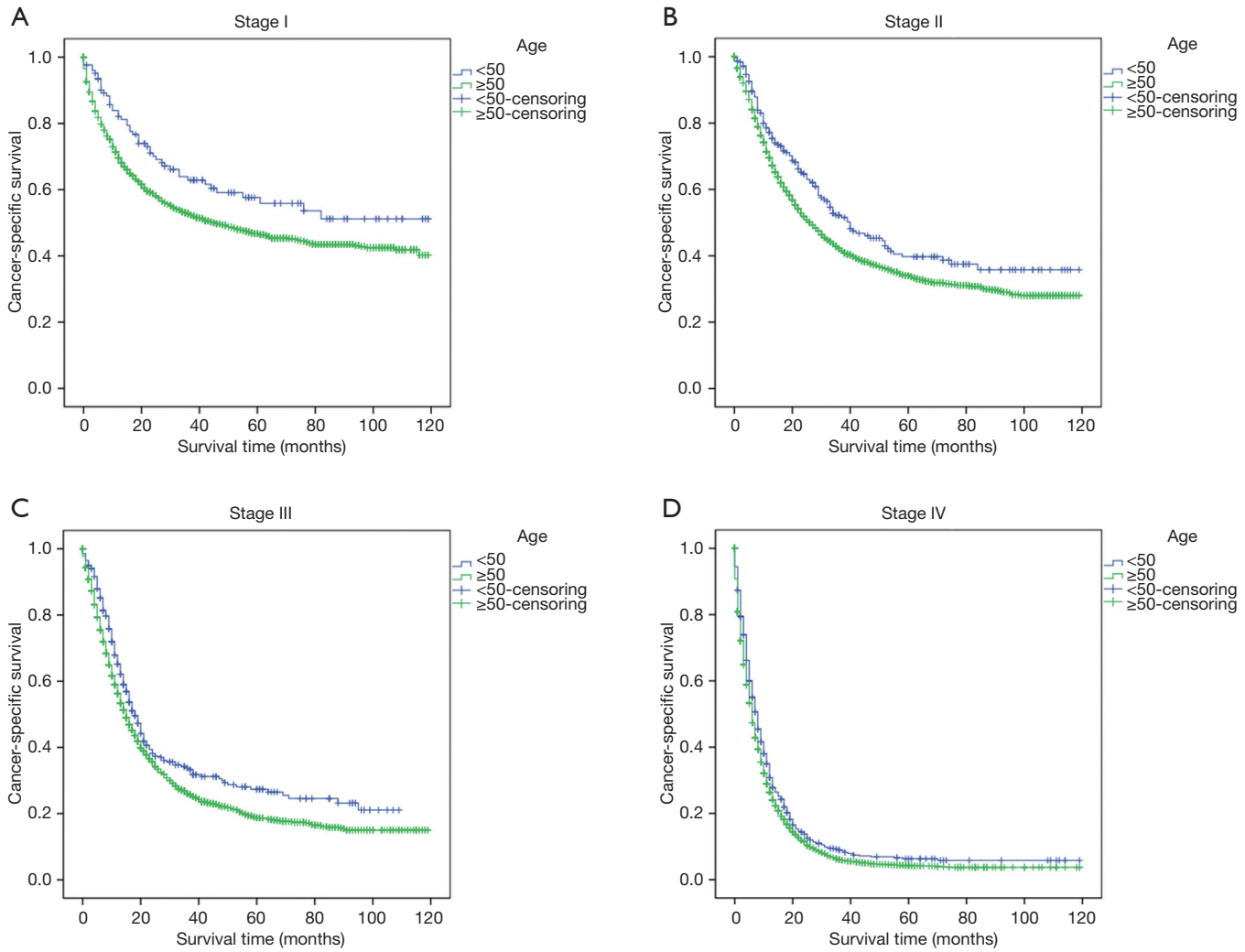

Figure 2 Kaplan-Meier curves comparing stage-wise esophageal cancer-specific survival between patients under 50 years and patients 50 years or older.

CI: 0.270–0.386; P<0.001) and radiation therapy (HR: 0.799; 95% CI: 0.696–0.917; P<0.001) were significant independent predictors of improved ECSS (*Table 3*).

Discussion

There has been a concomitant increase in EC diagnoses in younger patients along with the increased numbers of total esophageal adenocarcinoma diagnoses (6). This is a concern for clinicians because little is known about the clinicopathological characteristics and outcomes for EC in younger patients. Patients under 50-year-old have been considered the young patient cohort in many studies focused on EC (7,8,10,13,14) and other cancers (15,16). In this study, an analysis of the SEER database revealed that EC patients under 50 had distinctive clinicopathological characteristics and better survival outcomes compared to older patients. In addition, a multivariate analysis was also performed to identify independent prognostic factors in patients under 50.

A previous study compared EC in three age groups: under 49, between 50 and 69, and over 70 years (10). There were no significant differences among the three groups with regard to sex ratio, histological subtype, TNM classification or lymph node metastasis. In a separate report, Adam *et al.* reported esophagogastrectomy results in patients under 50 years compared with those between 50 and 69 or over 70 years (7). Again, no significant differences

Table 2 Multivariable analysis of ECSS in SEER population of patients with esophageal cancer

Characteristic	Univariable analysis (P)	Multivariable analysis		
		Hazard ratio	95% CI	P
Age	<0.001			
<50		0.881	0.824–0.943	<0.001
≥50		1 (reference)		
Gender	0.259			
Male				
Female				
Race	<0.001			
White		1 (reference)		
African-American		1.134	1.061–1.212	<0.001
other		0.937	0.856–1.025	0.155
Year	<0.001			
2004–2008		1.193	1.148–1.240	<0.001
2009–2013		1 (reference)		
Site of cancer	<0.001			
Upper esophagus		1 (reference)		
Middle esophagus		1.095	0.999–1.200	0.052
Lower esophagus		1.022	0.933–1.120	0.635
Differentiation grade	<0.001			
Grade I		1 (reference)		
Grade II		1.301	1.175–1.440	<0.001
Grade III or IV		1.631	1.475–1.802	<0.001
Histology	<0.001			
Squamous		1.059	1.002–1.119	0.042
Adenocarcinoma		1 (reference)		
Others		1.115	1.030–1.207	0.007
Stage	<0.001			
I		1 (reference)		
II		1.308	1.213–1.410	<0.001
III		2.015	1.875–2.166	<0.001
IV		2.681	2.504–2.870	<0.001
Surgery	<0.001			
Endoscopic		0.306	0.254–0.369	<0.001
Esophagectomy		0.346	0.328–0.365	<0.001
No		1 (reference)		
Radiation therapy	<0.001			
Yes		0.634	0.609–0.660	<0.001
No		1 (reference)		

NOS, not otherwise specified; ECSS, esophageal cancer-specific survival; CI, confidence interval; SEER, Surveillance, Epidemiology, and End Results.

were found in tumor pathology, stage, extent of resection, hospital mortality or survival. However, we report that EC patients under 50 are characterized by a higher proportion of male, African-Americans, lower esophageal disease, adenocarcinomas and later stages (III and IV) compared with older patients. Most strikingly, younger patients were more likely to have adenocarcinomas, which account for 72.5% of all diagnoses in this age group. Markar *et al.* (8) also found that patients under 50 years were more likely to have esophageal adenocarcinoma. This phenomenon may be related to obesity, chronic gastroesophageal reflux disease, smoking or a low intake of fruits and vegetables, which are the main risk factors for esophageal adenocarcinoma (1).

We performed stage-wise comparisons of OS and ECSS between the two groups, and the results showed that EC patients under 50 years old at diagnosis have significantly better OS and ECSS than older patients, despite more patients in the younger group presenting with more advanced-staged disease. This is consistent with the findings of Vallböhmer *et al.*, who reported that the 5-year survival rate of younger patients was significantly higher than elderly patients (12). However, several studies have suggested that there are no differences in the clinical characteristics or survival rates of younger or older EC patients (7,8,10,14). These studies may not have obtained statistically significant results due to small patient cohorts. In addition, a separate study indicated that younger esophageal adenocarcinoma patients had a poorer prognosis due to delayed diagnoses and more advanced disease (13).

Notably, we also identified age under 50 as an independent

Table 3 Multivariable analysis of ECSS in SEER population of patients under 50 with esophageal cancer

Characteristic	Univariable analysis (P)	Multivariable analysis		
		Hazard ratio	95% CI	P
Age	0.964			
<40				
≥40				
Gender	0.641			
Male				
Female				
Race	0.001			
White		1 (reference)		
African-American		1.508	1.238–1.837	<0.001
Other		0.999	0.723–1.380	0.995
Year	0.114			
2004–2008				
2009–2013				
Site of cancer	0.369			
Upper esophagus				
Middle esophagus				
Lower esophagus				
Differentiation grade	<0.001			
Grade I		1 (reference)		
Grade II		1.524	1.064–2.184	0.022
Grade III or IV		2.073	1.456–2.953	<0.001
Histology	0.163			
Squamous				
Adenocarcinoma				
Others				
Stage	<0.001			
I		1 (reference)		
II		1.454	1.033–2.046	0.032
III		2.217	1.602–3.067	<0.001
IV		2.96	2.163–4.051	<0.001
Surgery	<0.001			
Endoscopic		0.261	0.096–0.708	0.008
Esophagectomy		0.323	0.270–0.386	<0.001
No		1 (reference)		
Radiation therapy	<0.001			
Yes		0.799	0.696–0.917	<0.001
No		1 (reference)		

NOS, not otherwise specified; ECSS, esophageal cancer-specific survival; CI, confidence interval; SEER, Surveillance, Epidemiology, and End Results.

prognostic factor for better ECSS. This is similar to a report of a SEER analysis (17), in which age under 45 was found to be a better prognostic factor among all EC patients. The main reason behind these results may be related to the fact that younger patients tend to receive more aggressive treatments than older patients. Vallböhmer *et al.* have also reported that younger patients presented with significantly lower comorbidities and received more radio-neoadjuvant therapy (12). We also found that adenocarcinomas were associated with better survival rates than squamous cell carcinomas. This result suggested that younger EC patients are more likely to have adenocarcinoma, and therefore their prognosis is better than that of the older group. Furthermore, we found that younger patients were more likely to receive esophagectomy or radiotherapy. Mori *et al.* (10) also concluded that the rate of hospital death is significantly lower in younger patients compared with older patients. Therefore, younger patients are more likely to receive more aggressive therapy than older patients because they generally have a better medical performance status.

The multivariate analysis revealed that African-American heritage, grade III or IV, later stage and no surgical or radiation therapy were independent predictors of poor survival in both patients of all ages and those under 50 years. African-American patients had poorer survival rates than white patients, probably because they were less likely to undergo surgery (18) and were associated with lower socioeconomic status (19,20). Moreover, in younger patients, age, gender, year of diagnosis and histology

were not independent prognostic factors as they were in the overall EC population. The explanations for these differences are unclear, but it is possible that there were differences in the distribution of histologies across age groups or molecular markers across histologic subtypes that may have influenced prognosis (21).

There were some limitations in this study. First, it was a retrospective study that may result in certain biases. Second, the SEER database cannot collect all relevant clinical information to control for potential confounding variables, such as detailed treatment data, comorbidities, socioeconomic status, or known risk factors such as smoking and alcohol consumption. Furthermore, we also were unable to analyze some important factors such as chemotherapy and recurrence data on disease outcomes. Finally, these results may not be generalized to countries other than United States of America because ECs in the other countries may have a different distribution of histological types and may result from different environmental or genetic factors that are endemic to different ethnic backgrounds. Despite these limitations, SEER analysis provides a suitable opportunity to analyze a large number of patients under 50, especially since the majority of published data involving EC in younger patients were originated from single-institute retrospective studies with rather small patient numbers.

In conclusion, patients under 50 years old account for 8.37% of all EC cases and had distinctive clinicopathological characteristics compared to older patients. Despite presenting with stage III and IV disease more often, survival rates were better in the younger cohort. Additionally, prognostic factors for ECSS differed from those in the overall EC population. Finally, more investigations are needed to provide adequate data regarding young EC patients.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The study was approved by participating institutions through their respective institutional review boards.

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Supplementary

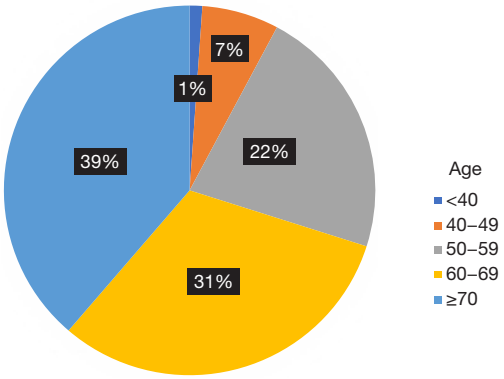

Figure S1 The distribution of each age.